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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY, COUNSEL, OR AGENT	CLASSIFICATION
09/214,913	03/16/1999	RICHARD ANTHONY GODWIN SMITH	033236/0110	8626

26633 7880 03/11/2003

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EXAMINER

HUYNH, PHUONG N.

ARTICLE PAPER NUMBER

1644

DATE MAILED: 03/11/2003

27

Please find below and or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/214.913

Applicant(s)

SMITH ET AL

Examiner

" Neon" Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 53-83 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 53-83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application)

Attachments

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4. <input type="checkbox"/> Interview Summary (PTO-413) Paper No. 5 |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-946) | 5. <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3. <input checked="" type="checkbox"/> Information Disclosure Statement (PTO-1449) Paper No. 5 26 | 6. <input type="checkbox"/> Other |

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DETAILED ACTION

1. The request filed on 12/18/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/214,913 is acceptable and a CPA has been established. An action on the CPA follows.
2. Claims 53-83 are pending.
3. Claims 53-83 are being acted upon in this Office Action.
4. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
5. Claims 53-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (A) a membrane localization reagent for directing a molecule to an outer membrane of a cell selected from the group consisting of SEQ ID NO: 37-41, wherein the membrane localization reagent is soluble and comprises (1) a lipophilic binding element consisting of aliphatic acyl group wherein the aliphatic acyl group is myristoyl group, (2) a hydrophilic peptide binding element consisting of basic amino acids selected from the group consisting of lysine or arginine bound to the lipophilic element and (3) a linker for covalently binding the molecule to the hydrophilic peptide binding element of the membrane localization reagent, (B) the said membrane localization reagent wherein the hydrophilic peptide binding element consisting of three to ten or four to seven residues such as lysine or arginine, (C) the said membrane localization reagent wherein the lipoprotein binding element consisting of 8 to 18 or 10 to 14 methylene units such as myristoyl, (D) the said membrane localization reagent wherein the linker is selected from the group consisting of a cysteine residue; an N-haloacetyl group wherein the halo is selected from the group consisting of chlorine, bromine, or iodine, a haloacetyl group wherein the halo is selected from the group consisting of chlorine, bromine, or iodine, or a haloacetyl group wherein the halo is selected from the group consisting of chlorine, bromine, or iodine, (E) the said membrane localization reagent wherein the molecule is a therapeutic

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agent selected from the group consisting of a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein kinase C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell. (F) A soluble compound that is directed to an outer membrane of a cell wherein the soluble compound consisting of (1) a therapeutic agent and (2) a membrane localization reagent selected from the group consisting of SEQ ID NO: 37-41, wherein the membrane localization reagent is soluble and comprises a lipophilic binding element consisting of aliphatic acyl group wherein the aliphatic acyl group is a myristoyl group, a hydrophilic peptide binding element consisting of basic amino acids selected from the group consisting of lysine or arginine bound to the lipophilic element, a linker for covalently binding the therapeutic agent to the hydrophilic peptide binding element of the membrane localization reagent, and (4) wherein the therapeutic agent is selected from the group consisting of a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein kinase C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell, **does not** reasonably provide enablement for *any* membrane localization reagent as set forth in claims 53-67 and *any* soluble compound that is directed to an outer membrane of a cell as set forth in claims 68-83 for directing *any* therapeutic agent such as the ones recited in claims 82-83 for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

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The specification discloses only a membrane localizing reagent consisting of only two heterologous membrane binding elements wherein one of the membrane binding elements is a myristoyl fatty acid with 12 methylene units and a basic polylysine amino acid sequence selected from the group consisting of GSSKSPSKKKKKKPGD, DGPKKKKKKKSPSKSSG, SPSNETPKKKKKKRFSFKKSG, DGPKKKKKKKSPSKSSK, SKDGKKKKKKKSKTK, DGPKKKKKKKSPSKSSGC, GSSKSPSKKKKKKPGDC, CDGPKKKKKKKSPSKSSK, or SKDGKKKKKKKSKTKC which is covalently associated with a soluble complement receptor (SCR1-3) (SEQ ID NOS: 7-14 and 17), or a conjugate of Streptokinase (SEQ ID NO: 21), or a plasminogen activator (SEQ ID NO: 22) for *in vitro* assays such as inhibition of complement-mediated lysis (pages 50-52), plasminogen activator assay (page 53) and erythrocyte binding assays (See pages 54-57).

The specification does not teach how to make and use *any* membrane localization reagent comprises *any* lipophilic binding element "comprising" *any* aliphatic acyl groups, *any* hydrophilic peptide binding element "comprising" basic amino acids, and a linker for binding *any* "molecule" to the hydrophilic peptide binding element of the membrane localization reagent because the term "comprising" is open-ended. It expands the "aliphatic acyl group" to include infinite number of carbon and undisclosed functional groups at either or both ends, it also expands the "hydrophilic binding elements" to include infinite number of undisclosed amino acids at either or both ends in addition to the basic amino acids that are already in the hydrophilic binding element of the localization reagent. There is insufficient guidance as to the structure of the membrane localizing reagent, let alone having the same function as SEQ ID NO: 37-41 such as directing any molecule to an outer membrane of a cell. Since the hydrophilic peptide element within the membrane localizing reagent are not enable, it follows that any hydrophilic peptide element "comprises" lysine or arginine residues such as three to ten or four to seven are not enabled.

It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al* teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al* teach further that GIF is unable to carry out the function of MIF

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in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, paragraph bridging columns in particular). Thus, knowing structure alone will not inherently tell us function (See figure, entire document). As such, further research would be required. Since the lipophilic binding element within the membrane localizing reagent are not enable, it follows that any peptide element such as the ones recited in claims 60-61 are not enable. It also follows that any lipophilic binding element "comprises" methylene units such as 8 to 18, 10 to 14 or myristoyl group are not enabled.

With regard to claim 66, there is insufficient guidance as to the structure and function of any "N-terminal blocking group", any "bond", any "fatty acid N-acyl group" at the N terminus or at an ϵ -amino group of a lysine residue for linking any molecule to the hydrophilic peptide binding element. Further, because the undisclosed "blocking group" at the N-terminus is used as blocking, it is not clear why one would link any molecule to the blocking group. Given the indefinite number of undisclosed membrane localization reagent having undisclosed N-terminal blocking group and fatty acyl group, there is insufficient working example demonstrating *any* undisclosed membrane localization reagent is effective for directing a molecule to an outer membrane of a cell. It is unpredictable which undisclosed membrane localization reagent would direct any molecule to an outer membrane of a cell for treating any disease.

With regard to any soluble compound that is directed to an outer membrane of a cell comprising any therapeutic agent, *any* membrane localizing reagent mentioned above, not only the membrane localizing reagent and linker mentioned above are not enabled, the term "therapeutic agent" encompasses indefinite number of undisclosed "therapeutic agent" that may not have an effect when directed to the cell membrane. The specification merely discloses only a specific antibody such as CD4, B7 CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell.

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localizing agent comprising the undisclosed hydrophilic binding element and the undisclosed lipophilic binding element and linker would effectively targeting the therapeutic agent to the cell membrane for treating any disease. In the absence of sufficient guidance as how to extrapolate data obtained from in vitro assays to the development of effective therapeutic agent direct to the outer membrane of a cell in vivo for treating any disease commensurate in scope with the claimed invention, it is not clear that the skilled artisan could predict the efficacy of the soluble compounds exemplified in the specification for in vivo treatment of any disease encompassed by the claims.

With regard to claims 82, the claim encompasses any antibody, any complement inhibitor, and any tissue plasminogen activator, there is insufficient guidance as to the binding specificity of any antibody, much less directing said antibody to the outer-membrane of any cell by linking to any undisclosed membrane localization reagent mentioned above. Other than the specific antibody, the specific complement inhibitor and the specific tissue plasminogen activator, there is insufficient guidance as to the structure of any complement inhibitor and any tissue plasminogen activator mentioned above, let alone having the same function as the specific complement inhibitor or plasminogen activator for treating all disease.

With regard to claim 83, the term "comprises" is open-ended. It expands the short consensus repeats 1-3 of long homologous Repeat A of complement receptor 1 to include additional amino acid at either or both ends of said repeat. There is insufficient guidance as to the structure of the undisclosed additional amino acid to be added, much less having the same function. Even if the term "comprising" is changed to "consisting of", the term Short Consensus Repeats 1-3 of Long Homologous Repeat A of complement receptor 1 without SEQ ID NO has no structure. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of any "short consensus repeats 1-3 of Long Homologous Repeat A of complement receptor 1", any "lipophilic binding element, any "hydrophilic peptide binding element", any "therapeutic agent", any "soluble compound", and still provide or maintain sufficient targeting specificity to an outer membrane of a cell for treating any disease is unpredictable and the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue. For these reasons, it would be inappropriate to grant the claims.

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In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat A of Complement Receptor 1 (CR1) conjugated to the specific membrane localization reagent (SMA1) mentioned above together forms the compound known as APT070. APT070 confers high affinity cell surface binding and has potent anti-complement activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad. Further, the term "comprising" is open-ended. It expands the basic element and the myristoyl lipophilic element to include addition element(s) at either or both ends. With the exception of the specific membrane localization reagent such as SEQ ID NO: 37-41 and the specific soluble compound comprising the specific therapeutic agent linked to the specific membrane localization reagent mentioned above, there is insufficient guidance, working example to demonstrate that *any* undisclosed membrane localization reagent comprising any lipophilic binding element, any hydrophilic peptide binding element, linker and any soluble compound or any therapeutic agent would be effective for treating any disease such as rheumatoid arthritis or complement mediated disease.

6. Claims 53-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification, and/or as being written in a manner that is not

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The specification does not reasonably provide a **written description** of *any* membrane localization reagent as set forth in claims 53-67 and *any* soluble compound that is directed to an outer membrane of a cell as set forth in claims 68-83 for directing *any* therapeutic agent such as the ones recited in claims 82-83 for treating *any* disease.

The specification discloses only a membrane localizing reagent consisting of only two heterologous membrane binding elements wherein one the membrane binding elements is a myristoyl fatty acid with 12 methylene units and a basic polylysine amino acid sequence selected from the group consisting of GSSKSPSKKKKKKPGD, DGPKKKKKKSPSKSSG, SPSNETPKKKKKKRFSFKKSG, DGPKKKKKKSPSKSSK, SKDGKKKKKKSKTK, DGPKKKKKKSPSKSSGC, GSSKSPSKKKKKKPGDC, CDGPKKKKKKSPSKSSK, or SKDGKKKKKKSKTKC which is covalently associated with a soluble complement receptor (SCR1-3) (SEQ ID NOS: 7-14 and 17), or a conjugate of Streptokinase (SEQ ID NO: 21), or a plasminogen activator (SEQ ID NO: 22) for **in vitro** assays such as inhibition of complement-mediated lysis (pages 50-52), plasminogen activator assay (page 53) and erythrocyte binding assays (See pages 54-57).

With the exception of the specific membrane localization reagent such as SEQ ID NO: 37-41 linked to the therapeutic agent such as a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, an urokinase, a streptokinase for directing said therapeutic agent to the outer membrane of a cell for the corresponding disease, there is inadequate written description about the structure associated with function of *any* membrane localization reagent comprises *any* lipophilic binding element "comprising" *any* aliphatic acyl groups, *any* hydrophilic peptide binding element "comprising" basic amino acids, and a linker for binding *any* "molecule" to the hydrophilic peptide binding element of the membrane localization reagent because the term "comprising" is open-ended. It expands the "aliphatic acyl group" to include infinite number of carbon or functional groups at either or both ends, it also expands the "hydrophilic binding elements" to include infinite number of undisclosed amino acids at either or both ends in addition to the basic amino acids that are already in the hydrophilic peptide binding element of the localization reagent. The specification does not provide any written description of the structure of the localization reagent that is associated with the function of directing a therapeutic agent to the outer membrane of a cell for the corresponding disease.

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described. It follows that any peptide element such as the ones recited in claims 60-61 are not adequately described. It also follows that any lipophilic binding element "comprises" methylene units such as 8 to 18, 10 to 14 or a myristoyl group is not adequately described.

With regard to claim 66, there is insufficient written description about the structure and function of any "N-terminal blocking group", any "bond", any "fatty acid N-acyl group" at the N terminus or at an ϵ -amino group of a lysine residue for linking any molecule to the hydrophilic peptide binding element. Further, the "blocking group" at the N-terminus is used for blocking; it is not clear why one would link any molecule to the blocking group.

With regard to any soluble compound that is directed to an outer membrane of a cell comprising any therapeutic agent, any membrane localizing reagent mentioned above, not only the membrane localizing reagent and linker mentioned above are not adequately described, the term "therapeutic agent" encompasses indefinite number of undisclosed "therapeutic agent" that may not have the same effect when directed to the cell membrane, let alone for treating any disease. The specification discloses only a specific antibody such as CD4, B7/CD28, CD3, TCR and CD11b (CR3), a specific complement inhibitor such as CD35, DAF (CD55), MCP (CD46), CD59, Factor H, a C4 binding protein, a protein C, leptin, IL-4, and a specific tissue plasminogen activator such as prourokinase, urokinase, and streptokinase for directing said therapeutic agent to the outer membrane of a cell. Given the indefinite number of soluble compound, there is insufficient written description about the structure and function of any undisclosed therapeutic agent, in turn, linked to any membrane localizing agent comprising the undisclosed hydrophilic binding element and the undisclosed lipophilic binding element and linker would effectively targeting the therapeutic agent to the cell membrane for treating any disease.

With regard to claims 82, the claim encompasses any antibody, any complement inhibitor, any tissue plasminogen activator, there is insufficient written description about the binding specificity of any antibody, much less directing said antibody to the outer-membrane of any cell by linking to any undisclosed any membrane localization reagent mentioned above. Other than the specific antibody, the specific complement inhibitor and the specific tissue plasminogen activator, there is insufficient written description about the structure of any complement inhibitor and any tissue plasminogen activator, let alone having the same function as

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additional amino acid at either or both ends of said repeat. There is inadequately written description about the structure of the undisclosed additional amino acid, much less having the same function. Even if the term "comprising" is changed to "consisting of", the term Short Consensus Repeats 1-3 of Long Homologous Repeat A of complement receptor 1 without SEQ ID NO has no structure.

With the exception of the specific membrane localization reagent such as SEQ ID NO: 37-41 and the specific soluble compound comprising the specific therapeutic agent linked to the specific membrane localization reagent mentioned above, there is inadequate written description of *any* additional representative species of membrane localization reagent, lipophilic binding element, hydrophilic peptide binding element, linker and soluble compound, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat A of Complement Receptor 1 (CR1) conjugated to the specific membrane localization reagent (SMA1) mentioned above together forms the compound known as APT070. APT070 confers high affinity cell surface binding and has potent anti-complement activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad to read on the reference membrane localization reagent.

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localization reagent such as SEQ ID NO: 37-41 and the specific soluble compound comprising the specific therapeutic agent linked to the specific membrane localization reagent mentioned above, there is a lack of a written description of *any* additional representative species of membrane localization reagent, lipophilic binding element, hydrophilic peptide binding element, linker and soluble compound, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 53, 60-61, 64, 68, 75 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "GSSKSPSKKKKKKPGD (SEQ ID NO: 39)" in claims 60, 61, 75 and 76 is erroneous because "GSSKSPSKKKKKKPGD" should have been SEQ ID NO: 38 according to the sequence listing submitted on Sept 13, 2000 and the specification on page 6. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The recitation of "SPSNETPKKKKKKRFSFKKSSG (SEQ ID NO: 41)" in claims 60 and 75 is indefinite and ambiguous because (1) there is an extra "S" in the sequence and (2) said sequence should have been SEQ ID NO: 39.

The recitation of "DGPKKKKKKSPSKSSK (SEQ ID NO: 43)" in claims 60 and 75 is in error because it should have been SEQ ID NO: 40.

The recitation of "SKDGKKKKKKSKTK (SEQ ID NO: 45)" in claims 60 and 75 is in error because it should have been SEQ ID NO: 41 according to the sequence listing submitted on Sept 13, 2000 and the specification on page 6. Appropriate correction is required.

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9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 53-55, 57-58, and 62-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Sigal *et al.* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892).

Sigal *et al* teach a membrane targeting agent such (Myr-GSSKSKPKDPSQRRR) wherein the reference agent consisting of a myristoyl group (Myr) which is a lipophilic binding element consisting of aliphatic acyl group (12 methylene units) linked to a hydrophilic amino acid sequence rich with positively charged residues such as lysine and arginine (GSSKSKPKDPSQRRR) and a linker such as a peptide bond that binds to a molecule such as a phosphatidyletholine/phosphatidylserine (artificial membrane) (See page 12253, column 1, in particular). The reference membrane localization reagent contains at least five basic residues such as lysine. The term "comprising" is open-ended. It expands the hydrophilic peptide binding elements to include additional amino acid to read on the reference peptide binding element. Claims 62-63 are included in this rejection because the reference lipophilic binding element myristic acid contains 12 methylene units which are within the claimed 8 to 18 or 10 to 14 methylene units. Sigal *et al* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat (A) (EC) and (B) (R) (SMA1) (SMA2) (SMA3) (SMA4) (SMA5) (SMA6) (SMA7) (SMA8) (SMA9) (SMA10) (SMA11) (SMA12) (SMA13) (SMA14) (SMA15) (SMA16) (SMA17) (SMA18) (SMA19) (SMA20) (SMA21) (SMA22) (SMA23) (SMA24) (SMA25) (SMA26) (SMA27) (SMA28) (SMA29) (SMA30) (SMA31) (SMA32) (SMA33) (SMA34) (SMA35) (SMA36) (SMA37) (SMA38) (SMA39) (SMA40) (SMA41) (SMA42) (SMA43) (SMA44) (SMA45) (SMA46) (SMA47) (SMA48) (SMA49) (SMA50) (SMA51) (SMA52) (SMA53) (SMA54) (SMA55) (SMA56) (SMA57) (SMA58) (SMA59) (SMA60) (SMA61) 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activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad to read on the reference membrane localization reagent as taught by Sigal *et al* or Hancock *et al*. Further, the term "comprising" is open-ended. It expands the basic element and the myristoyl lipophilic element to include addition element such as carbon or other undisclosed functional groups at either or both ends. It also expands the basic element to include additional undisclosed amino acids at either or both ends, much less having the same function as APTO70.

11. Claims 53-59, 62-63, and 66 are rejected under 35 U.S.C. 102(b) as being anticipated by Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892).

Hancock *et al* teach a membrane targeting agent such as a lipophilic peptide binding element comprising aliphatic acyl group such as palmitoyl (14 methylene units), farnesyl or geranylgeranyl, a hydrophilic peptide binding element such as basic amino acids such as six lysine or six arginine and a linker such as a bond that links the reference hydrophilic element to a molecule such as p21K-ras(B) (see abstract, in particular). Hancock *et al* teach polyarginine domain can function as a plasma membrane targeting motif and replacing the polyarginine domain with the polylysine domain is still biological active (See abstract, in particular). The term "comprising" is open-ended. It expands the lipophilic peptide binding element to include additional carbon at either end to read on the reference farnesyl or geranylgeranyl of the lipophilic peptide binding element. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat (LTR) of HIV-1, which is a protein that is a member of the

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activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad to read on the reference membrane localization reagent as taught by Sigal *et al* or Hancock *et al*. Further, the term "comprising" is open-ended. It expands the basic element and the myristoyl lipophilic element to include addition element such as carbon or other undisclosed functional groups at either or both ends. It also expands the basic element to include additional undisclosed amino acids at either or both ends, much less having the same function as APT070.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 53, 67, 68-70, 72-73, 77-78 and 80-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) in view of Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892).

The teachings of Sigal *et al* have been discussed supra.

The claimed invention as recited in claim 67 differs from the teachings of the reference only that the membrane localization reagent wherein the molecule is a therapeutic agent.

[Signature]

[Signature]

[Signature] The membrane localization reagent is soluble

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and comprises (a) lipophilic binding element comprising aliphatic acyl groups; (b) a hydrophilic peptide binding element comprising basic amino acids, wherein the hydrophilic binding element is bound to the lipophilic element and (c) a linker that covalently binds the therapeutic agent to the hydrophilic peptide binding element of the membrane localization reagent from the soluble compound.

The claimed invention as recited in claim 69 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises lysine residues.

The claimed invention as recited in claim 70 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten lysine residues.

The claimed invention as recited in claim 72 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises arginine residues.

The claimed invention as recited in claim 73 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten arginine residues.

The claimed invention as recited in claim 77 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 8 to 18 methylene units.

The claimed invention as recited in claim 78 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 10 to 14 methylene units.

The claimed invention as recited in claim 80 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises myristoyl.

The claimed invention as recited in claim 81 differs from the teachings of the reference only that the soluble compound wherein the linker is a bond.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of combination of ligands with therapeutic compounds is not disclosed.

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al teach the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ligand such as transferrin as taught by Citro *et al* for the targeting agent such (Myr-GSSKSKPKDPSQRRR) wherein the reference agent consisting of a myristoyl group (Myr) which is a lipophilic binding element consisting of aliphatic acyl group (12 methylene units or 14 carbons) linked to a hydrophilic amino acid sequence rich with positively charged residues such as lysine and arginine (GSSKSKPKDPSQRRR) and a linker such as a cysteine disulfide peptide bond that binds to any drug for directing the drug to the outer membrane as taught by Citro *et al* and Sigal *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Citro *et al* teach the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat A of Complement Receptor 1 (CR1) conjugated to the specific membrane localization reagent (SMA1) mentioned above together forms the compound known as APT070. APT070 confers high affinity cell surface binding and has potent anti-complement activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad to read on the reference membrane localization reagent as taught by Sigal *et al* or Hancock *et al*. Further, the term "comprising" is open-ended and does not require the inclusion of the elements recited in the

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ends. It also expands the basic element to include additional undisclosed amino acids at either or both ends, much less having the same function as APT070.

15. Claims 53, 67-74, 77-78 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) in view of Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892).

The teachings of Hancock et al have been discussed supra.

The claimed invention as recited in claim 67 differs from the teachings of the reference only that the membrane localization reagent wherein the molecule is a therapeutic agent.

The claimed invention as recited in claim 68 differs from the teachings of the reference only that the soluble compound that is directed to an outer membrane of a cell comprises a therapeutic agent, a membrane localization wherein the membrane localization reagent is soluble and comprises (a) lipophilic binding element comprising aliphatic acyl groups; (b) a hydrophilic peptide binding element comprising basic amino acids, wherein the hydrophilic binding element is bound to the lipophilic element and (c) a linker that covalently binds the therapeutic agent to the hydrophilic peptide binding element of the membrane localization reagent from the soluble compound.

The claimed invention as recited in claim 69 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises lysine residues.

The claimed invention as recited in claim 70 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises three to ten lysine residues.

The claimed invention as recited in claim 71 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises four to seven lysine residues.

The claimed invention as recited in claim 72 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises arginine residues.

The claimed invention is directed to a method for determining a value of a function of a variable, the method comprising:

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The claimed invention as recited in claim 74 differs from the teachings of the reference only that the soluble compound wherein the hydrophilic peptide binding element comprises four to seven arginine residues.

The claimed invention as recited in claim 77 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 8 to 18 methylene units.

The claimed invention as recited in claim 78 differs from the teachings of the reference only that the soluble compound wherein the lipophilic binding element comprises 10 to 14 methylene units.

The claimed invention as recited in claim 81 differs from the teachings of the reference only that the soluble compound wherein the linker is a bond or a cysteine residue.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myc antisense oligonucleotide to a ligand such as transferrin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ligand as taught by Citro *et al* for the targeting agent comprising the lipophilic peptide binding element such as the aliphatic acyl group of palmitoyl which has 14 methylene units or farnesyl or geranylgeranyl linked to a hydrophilic peptide binding element such as six basic amino acids from the group of lysine or arginine and a linker such as a peptide bond or disulfide bond via cysteine that links any drug for directing the drug to the outer membrane as taught by Citro *et al* and Sigal *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index,

maximizes the therapeutic benefit without inducing unacceptable toxicity.

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replacing the polylysine domain with polyarginine still can function as a plasma membrane targeting domain motif (See abstract, in particular).

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat A of Complement Receptor 1 (CR1) conjugated to the specific membrane localization reagent (SMA1) mentioned above together forms the compound known as APT070. APT070 confers high affinity cell surface binding and has potent anti-complement activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad to read on the reference membrane localization reagent as taught by Sigal *et al* or Hancock *et al*. Further, the term "comprising" is open-ended. It expands the basic element and the myristoyl lipophilic element to include addition element such as carbon or other undisclosed functional groups at either or both ends. It also expands the basic element to include additional undisclosed amino acids at either or both ends, much less having the same function as APT070.

16. Claims 68 and 82-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) or Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) each in view of US Pat No. 5,472,939, (of record, Dec 1995, PTO 892) and Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892).

The teachings of Sigal *et al* and Hancock *et al* have been discussed supra.

The claimed invention of claim 82 differs from the teachings of the references only that the soluble compound wherein the therapeutic agent is a complement inhibitor.

The claimed invention is not obvious over the references as discussed supra.

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The '939 patent teaches a soluble complement regulatory protein sCRI which has a short consensus structure motif that binds to a complement component for reducing tissue damage associated with myocardial infarction (See column 8, lines 15-40, column 9, lines 29 and 43-44, column 67, 68, 69 and Abstract, in particular). The '939 patent further teaches a fusion protein comprising a portion of the CR1 sequence plus a non-CR1 sequence (See column 21, lines 39-42). The '939 patent teach other deletion mutants of CR1 which are functional derivatives (See column 16, lines 41-58, in particular).

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myc antisense oligonucleotide to a ligand such as transferrin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently link the membrane localization reagent as taught by Sigal *et al* or Hancock *et al* with the soluble complement inhibitor or short consensus repeat 1-3 of Long Homologous Repeat A of Complementary Receptor 1 for directing said soluble complement inhibitor to the outer membrane of a cell as taught by Sigal *et al*, or Hancock *et al* to improve the therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular) as taught by Citro *et al*.

One having ordinary skill in the art would have been motivated to do this because the '939 patent teaches that a soluble CR1 molecule or fusion protein may be used to treat damage caused by a myocardial infarction associated with inflammation and inappropriate complement activation (See column 8, lines 15-40, column 9, lines 29 and 43-44, column 67, 68, 69 and Abstract, in particular). Sigal *et al* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Hancock *et al* teach that polyarginine domain can function as a plasma membrane targeting motif (see Hancock *et al*, supra, at 12253, column 2, in particular).

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of targeting delivery of any drugs would improve therapeutic index having maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

17. Claims 68 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) or Hancock *et al* (EMBO J 10(13): 4033-9, Dec 1991; PTO 892) each in view of Citro *et al* (Dis Colon Rectum 37(2): 127-32, abstract, Feb 1994; PTO 892) and EP 0,207,589 A1, (Jan 1987, PTO 892) or EP 0,155,387 A2 (Sept 1985, PTO 892) or U S Pat No 5,326,700 (July 1994, PTO 892).

The teachings of Sigal *et al* and Hancock *et al* have been discussed supra.

The claimed invention of claim 82 differs from the teachings of the references only that the soluble compound wherein the therapeutic agent is a tissue plasminogen activator, a prourokinase or streptokinase.

Citro *et al* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myc antisense oligonucleotide to a ligand such as transferrin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al* teach that the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

The EP 0207,589 A1 patent teaches tissue type plasminogen activator, functional derivatives thereof such as urokinase (see page 10, in particular) and pharmaceutical compositions for treatment of thrombotic diseases (See page 6, lines 39-42).

The EP 0,155,387 A2 patent teaches hybrids of plasmin linked to urokinase plasminogen activator B-chain (See page 11, claims 1-4 of EP 0,155,387 A2 and a pharmaceutical composition for treating thrombotic diseases (See pages 6-7, in particular).

The '700 patent teaches a tissue plasminogen activator having an amino acid sequence identical to SEQ ID NO: 22 of the instant application (See column 39, SEQ ID NO: 16 of '700, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently link the therapeutic agent to the ligand as taught by Citro *et al*.

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plasminogen activator B-chain as taught by the EP 0,155,387 A2 patent or the tissue plasminogen activator as taught by the '700 patent for directing said soluble complement inhibitor to an outer membrane of a cell as taught by Sigal *et al.*, Hancock *et al.* to improve therapeutic index by having maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular) as taught by Citro *et al.*

One having ordinary skill in the art would have been motivated to do this because the the tissue type plasminogen activator, or functional derivatives thereof and hybrid as taught by the EP 0207,589 A1 patent or the EP 0,155,387 A2 patent or the plasminogen activator as taught by the '700 patent can be used for treating thrombotic disease. Citro *et al.* teach that the advantage of targeting delivery of any drugs would improve therapeutic index having maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular). Sigal *et al.* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Hancock *et al.* teach that the polyarginine domain can function as a plasma membrane targeting motif and replacing the polyarginine domain with the polylysine domain is still biological active (See abstract, in particular).

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat A of Complement Receptor 1 (CR1) conjugated to the specific membrane localization reagent (SMA1) mentioned above together forms the compound known as APT070. APT070 confers high affinity cell surface binding and has potent anti-complement activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted Declaration fully explains the motivation for the

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include addition element such as carbon or other undisclosed functional groups at either or both ends. It also expands the basic element to include additional undisclosed amino acids at either or both ends, much less having the same function as APTO70.

18. Claims 53, 66, 68 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al.* (of record, Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) or Hancock *et al.* (EMBO J 10(13): 4033-9, Dec 1991, PTO 892) each in view of EP 0109,653 (May 1984; PTO 892) or EP 0152736 (of record, Aug 1985, PTO 892).

The teachings of Sigal *et al.* and Hancock *et al.* have been discussed supra.

The claimed invention of claims 66 and 81 differs from the teachings of the references only that the soluble compound or therapeutic agent wherein the linker is a cysteine residue, an amide at the C-terminus, a haloacetyl group where halo signifies chlorine, bromine or iodine or an ϵ amino acid group of a lysine residue.

Citro *et al.* teach a method of delivering therapeutic compounds such as drugs and oligodeoxynucleotides to a cell using ligands for cell receptors to deliver any drugs to the cell. The reference method of conjugating a drug such as c-myc antisense oligonucleotide to a ligand such as transferrin, folic acid or steroid covalently linked to a polylysines through disulfide bridge (cysteine) and used as a carrier to direct the drug to the cell (See abstract, in particular). Citro *et al.* teach the advantage of targeting delivery of any drugs improves therapeutic index, maximum therapeutic benefit without inducing unacceptable toxicity (See abstract, in particular).

The EP 0152736 patent teaches various linker such as a N-haloacetyl group where halo signifies chlorine, bromine or iodine for preparing various urokinase complex which is useful as a thrombolytic agent (page 17, line 10; abstract, in particular)

The EP 0152736 patent teaches an enzyme-protein conjugate using bridging groups having a formula of (I): -A-R-B- in which each of A and B, which may be the same or different, represents -CO-, -C(-NH₂)-, maleimido group which contains a cysteine, a sulfahydryl group such as -S-, or a bond and R is a bond or a linking group containing one or more -(CH₂)- or meta-, ortho- or para- disubstituted phenyl units optionally together with a hydrophobic portion; the R is selected from -(CH₂)_r-, -(CH₂)_p-S-S-(CH₂)_q- (See pages 2-3, 31, in particular). The EP 0152736 patent further teaches that the linker is a cysteine residue, an amide at the C-terminus, a haloacetyl group where halo signifies chlorine, bromine or iodine or an ϵ amino acid group of a lysine residue.

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the linker as taught by Sigal *et al* or Hancock *et al* for the N-haloacetyl group as taught by the EP 0152736 patent or the cysteine maleimido group as taught by the EP 0152736 patent for directing the soluble compound or therapeutic agent to the outer membrane as taught by Citro *et al*, Sigal *et al* and Hancock *et al*.

One having ordinary skill in the art would have been motivated to use the bridging group as taught by the EP 0152736 patent because the derivative or conjugates made using these bridging group are suitable for pharmaceutical compositions (See page 11, in particular). The EP 0152736 patent teaches various linker such as a N-haloacetyl group where halo signifies chlorine, bromine or iodine for preparing various urokinase complex which is useful as a thrombolytic agent (page 17, line 10, abstract, in particular).

Applicants' arguments and the declaration filed by Richard Anthony Godwin Smith filed 12/18/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention was inspired by the myristoyl-electrostatic switch, (2) Example 2 of the application discloses a specific membrane localization reagent that has a combination of myristoyl lipophilic element (SMA1) which address the cell bilayers, a basic element of six lysine residues (SMA2) which address the acidic heads of the phospholipids and the two are bound to a linker, (3) Example 8 of the specification discloses SCR1-3 of long terminal repeat A of Complement Receptor 1 (CR1) conjugated to the specific membrane localization reagent (SMA1) mentioned above together forms the compound known as APT070. APT070 confers high affinity cell surface binding and has potent anti-complement activity as measured by the inhibition of hemoglobin release and protect a compromised rat from the acute effect of complement activation, where complement plays a role in rheumatoid arthritis.

In response, the newly submitted claims are still overly broad to read on the reference membrane localization reagent as taught by Sigal *et al* or Hancock *et al*. Further, the term "comprising" is open-ended. It expands the basic element and the myristoyl lipophilic element to include addition element such as carbon or other undisclosed functional groups at either or both ends. It also expands the basic element to include additional undisclosed amino acids at either or both ends, much less having the same function as APT070.

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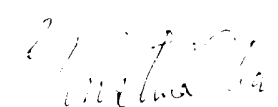
19. Claim 60 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
20. No claim is allowed.
21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
22. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

March 10, 2003


CHRISTINA CHAN
PATENT EXAMINER
MAR 10 2003